EMBRYONIC STEM CELL RESEARCH: A NEW FIELD WITH TREMENDOUS PROMISE

Scientists have only begun to investigate the therapeutic potential of human embryonic stem cells. These stem cells could be a boon to medical research and treatment in many ways—as replacement cells for those that have been lost or destroyed because of disease, as tools for studying early events in human development (shedding light on birth defects), as test systems for new drug therapies, to screen potential toxins, and as vehicles or "vectors" to deliver genes that could correct defects. Embryonic stem cells could lead to treatments for diseases that afflict up to 100 million Americans, including Alzheimer's and Parkinson's disease, diabetes, cancer, heart disease, spinal cord injuries, and other debilitating conditions.

Human embryonic stem cells were isolated in 1998, and since this time academic researchers have been hampered by limitations on federal funding for studying them. Nonetheless, in that short time scientists have already made important progress in learning about their properties and optimizing conditions for creating new lines. In addition, a number of experiments have already produced encouraging results regarding their therapeutic potential.

2002

HUMAN EMBRYONIC STEM CELLS ALLOW PARALYZED RATS TO WALK

Researchers at the University of California-Irvine coax human embryonic stem cells to develop into brain cells, which are then injected into rats with damaged spinal cords. After nine weeks, the rats are able to walk again.

Preliminary findings presented at annual meeting of Society for Neuroscience, 2002.Work to be published in journal in early 2005.

EMBYRONIC STEM CELLS RELIEVE DIABETES SYMPTOMS IN MICE

Stanford scientists use special chemicals to transform undifferentiated embryonic stem cells of mice into cell masses that resemble islets found in the mouse pancreas. When this tissue is transplanted into diabetic mice, it produces insulin in response to high glucose levels in the animals.

Growth inhibitors promote differentiation of insulin-producing tissue from embryonic stem cells.
Hori Y, Rulifson IC, Tsai BC, Heit JJ, Cahoy JD, Kim S.. *Proc Natl Acad Sci U S A.* 2002 Dec 10;99(25):16105-10.

HUMAN EMBRYONIC STEM CELLS GROWN WITHOUT MOUSE CELL TISSUE

Researchers in Singapore grow human embryonic stem cells without using a layer of animal cells or animal protein factors to maintain them, an important breakthrough if embryonic stem cells are to be used for treating type 1 diabetes and other diseases in humans. The ability to create large numbers of human stem cells without danger of contamination by animal pathogens is essential for stem cell therapies to be deemed safe by the U.S. Food & Drug Administration.

Human feeders support prolonged undifferentiated growth of human inner cell masses and embryonic stem cell. Richards M, Fong CY, Chan WK, Wong PC, Bongso A. *Nature Biotechnology* 2002 Sep;20(9):933-6

RESEARCHERS USE EMBRYONIC STEM CELLS TO CORRECT GENETIC DEFECT IN MICE

Researchers at the Whitehead Institute in Cambridge, Massachusetts, use embryonic stem cells created through somatic cell nuclear transfer (SCNT) to cure a genetic defect in mice. The method allows them to create embryonic stem cells identical to the animal, correct the genetic defect in the cells in a petri dish, and then inject the cells back inside the mouse. The experiment shows proof-of-principle for using SCNT to cure disease.

Correction of a genetic defect by nuclear transplantation and combined cell and gene therapy.
Rideout WM 3rd, Hochedlinger K, Kyba M, Daley GQ, Jaenisch R. *Cell* 2002 Apr 5;109(1):17-27

JDRF Juvenile Diabetes Research Foundation International
dedicated to finding a cure

2003

RESEARCHERS ALTER GENETIC MAKEUP OF HUMAN EMBRYONIC STEM CELLS

Scientists at the University of Wisconsin-Madison report developing methods for recombining segments of DNA within human embryonic stem cells. The advance should make it possible to manipulate any small part of the human genome to study gene function and mimic human disease in the laboratory dish. *Washington Post* science writer Rick Weiss says the work is a step toward being able to rebuild or regenerate parts of the human body by transplanting either stem cells or tissues grown from stem cells into patients. Tweaking the cells with specific genetic changes might enhance their true therapeutic potential or make them more compatible with patients' immune systems.

Homologous recombination in human embryonic stem cells. Zwaka, T. P., and Thomson, J. A. *Nat Biotechnol (2003). 21, 319-321.*

'MASTER' STEM CELL GENE IDENTIFIED

Research teams in Japan and Scotland identify a gene in embryonic stem cells that allows them to retain their unique ability to regenerate and develop into any cell type. The discovery should be an important advance in efforts to coax stem cells to differentiate into specific types — such as insulin-secreting beta cells — for the treatment of disease.

Functional expression cloning of Nanog, a pluripotency sustaining factor in embryonic stem cells.
Chambers I, Colby D, Robertson M, Nichols J, Lee S, Tweedie S, Smith A. *Cell*. 2003 May 30;113(5):643-55.

The homeoprotein Nanog is required for maintenance of pluripotency in mouse epiblast and ES cells.
Mitsui K, Tokuzawa Y, Itoh H, Segawa K, Murakami M, Takahashi K, Maruyama M, Maeda M, Yamanaka S. *Cell*. 2003 May 30;113(5):631-42.

RESEARCHER CREATES 17 NEW EMBRYONIC STEM CELL LINES WITH PRIVATE FUNDING

Harvard University molecular biologist Douglas Melton, Ph.D., announces in November that his lab developed 17 human embryonic stem cell lines and plans to provide the cells to the American Type Culture Collection in Virginia and the UK Stem Cell Bank for distribution to researchers worldwide. To put this accomplishment in context, U.S. policy at the time had resulted in only 12 embryonic stem cell lines available to federally-funded researchers.

Derivation of embryonic stem-cell lines from human blastocysts. Cowan CA, Klimanskaya I, McMahon J, Atienza J, Witmyer J, Zucker JP, Wang S, Morton CC, McMahon AP, Powers D, Melton DA.
N Engl J Med. 2004 Mar 25;350(13):1353-6.

STUDY SHOWS BONE-MARROW ADULT STEM CELLS DO NOT TRANSFORM

Researchers at the University of California at San Francisco (UCSF) and four other institutions report that stem cells from adult bone marrow do not appear to have the ability to transform into other cell types, contradicting earlier studies suggesting the cells have this capacity. The new finding suggests that scientists may have overstated the older results, and that only embryonic stem cells have the potential to regenerate ailing hearts, livers, and brains.

Fusion of bone-marrow-derived cells with Purkinje neurons, cardiomyocytes and hepatocytes.
Nature. 2003 Oct 30;425(6961):968-73. Epub 2003 Oct 12

2004

SCIENTISTS FIND NEW INSULIN-PRODUCING BETA CELL FORMATION DOES NOT RELY ON ADULT STEM CELLS

Researchers at Harvard University and the Howard Hughes Medical Institute (HHMI) find in mice that new insulin-secreting beta cells in the pancreas are formed through the replication of existing beta cells rather than the differentiation of adult stem cells. This establishes firmly that adult stem cells in the pancreas do not contribute to new beta cell formation in the mouse—and strongly suggests that embryonic stem cells may prove to be the only stem cells that will be useful in the laboratory to generate beta cells for the treatment of type 1 diabetes.

Adult pancreatic beta cells are formed by self-duplication rather than stem-cell differentiation Dor Y, Brown J, Martinez OI, Melton DA.
Nature. 2004 May 6;429(6987):41-6.

HUMAN EMBRYONIC STEM CELLS BECOME BEATING HEART CELLS

Researchers at the Technion Institute in Israel allow human embryonic stem cells to spontaneously
develop into beating heart cells, then transplant the cells into a cluster of live rat heart cells in a lab dish. Within 24 hours, the combined masses begin beating at the same rate. The human heartcells also perform well when transplanted into pigs with a heart condition.

Electromechanical integration of cardiomyocytes derived from human embryonic stem cells. Kehat I, Khimovich L, Caspi O, Gepstein A, Shofti R, Arbel G, Huber I, Satin J, Itskovitz-Eldor J, Gepstein L. *Nature Biotechnolology* 2004 Oct;22(10):1282-9. Epub 2004 Sep 26

HUMAN EMBRYONIC STEM CELLS BECOME EYE CELLS CRUCIAL TO VISION

Researchers at Advanced Cell Technology allow human embryonic stem cells to spontaneously develop into retinal pigment epithelial cells (RPE cells), which are critical to vision. This could lead to treatments for age-related macular degeneration, the leading cause of vision loss in people 60 or older. One of the scientists in the study says the company hopes to test the cells in animals during the next year, and, if they prove successful, get permission to conduct trials in humans with RPE-related vision loss.

Derivation and comparative assessment of Retinal Pigment Epithelium from human embryonic stem cells using transcriptomics. Klimanskaya I, Hipp J, Rezai K, West M, Atala A, Lanza R. *Cloning and Stem Cells* Vol. 6, No. 3, 2004.

EMBRYONIC STEM CELLS PRODUCE HEALING COMPOUNDS THAT CORRECT GENETIC DEFECT

Researchers at Sloan-Kettering Cancer Center in New York find that embryonic stem cells produce proteins that can help ailing organs repair themselves. Mouse embryonic stem cells injected into pregnant mice carrying a genetic heart defect secreted compounds that corrected the defect in the embryos. The animals that were born had normally functioning hearts. This capacity "expands the potential therapeutic repertoire" of embryonic stem cells, says Dr. Kenneth Chien of the University of California, San Diego, in an accompanying commentary.

Rescue of cardiac defects in id knockout embryos by injection of embryonic stem cells. Fraidenraich D, Stillwell E, Romero E, Wilkes D, Manova K, Basson CT, Benezra R. *Science*, 2004 Oct 8;306(5694):247-52

HUMAN EMBRYONIC STEM CELLS RELIEVE SYMPTOMS OF PARKINSON'S DISEASE IN RATS

Israeli scientists coax human embryonic stem cells to become nerve cells that produce the chemical dopamine. When the resulting cells are transplanted into rats with symptoms of Parkinson's disease, the animals had slightly improved mobility.

Transplantation of human embryonic stem cell-derived neural progenitors improves behavioral deficit in Parkinsonian rats. Ben-Hur T, Idelson M, Khaner H, Pera M, Reinhartz E, Itzik A, Reubinoff BE. *Stem Cells*. 2004;22(7):1246-55.

RESEARCHERS DEVELOP 'DISEASE-SPECIFIC' EMBRYONIC STEM CELL LINES

At the annual meeting of the International Society for Stem Cell Research (ISSCR), research teams from institutions in Chicago and in Israel report developing stem cell lines from embryos carrying a genetic disorder, including three forms of muscular dystrophy. Some couples who undergo in vitro fertilization treatment have a family history of genetic disorders that cause disease. Because of recent technological developments, these couples can use pre-implantation genetic diagnosis to identify which of their embryos created in the laboratory are unaffected by such disorders and thus appropriate for reproductive use. Embryos identified as having serious genetic disorders, while not usable for reproductive purposes and normally discarded, can, however, be used as the source for human embryonic stem cell lines that will have these disease characteristics. Many human disorders, such as muscular dystrophy and cystic fibrosis, arise from a defect in a single gene. In order to understand how the defect contributes to disease, and how to develop ways to correct it, scientists benefit from the ability to study cells carrying the defective gene from the earliest stage of development. This is especially useful in cases where animal models for a disease do not faithfully simulate the symptoms and conditions that occur in humans.
Boston Globe, June 9, 2004.

RESEARCHERS CREATE HUMAN EMBRYONIC STEM CELLS THROUGH SCNT FOR FIRST TIME

Researchers in South Korea produce a human embryonic stem cell line through the use of somatic cell nuclear transfer, a procedure commonly known as "therapeutic cloning." The creation of human embryonic stem cells through this method provides proof-of-principle that this technique might someday provide stem cell lines that could be used to develop curative therapies for a wide range of diseases.

Evidence of a pluripotent human embryonic stem cell line derived from a cloned blastocyst.
Hwang WS, Ryu YJ, Park JH, Park ES, Lee EG, Koo JM, Jeon HY, Lee BC, Kang SK, Kim SJ, Ahn C, Hwang JH, Park KY, Cibelli JB, Moon SY. *Science* 2004 Mar 12;303(5664):1669-74. Epub 2004 Feb 12.

2005

FEDERALLY APPROVED STEM CELL LINES ARE CONTAMINATED

Researchers at the University of California, San Diego find conclusive proof of what scientists suspected for years: All human embryonic stem cells available for use in federally funded research are contaminated with animal molecules from the culture medium used to sustain them. The finding, reported online January 23 in the journal *Nature Medicine*, strongly suggests that these stem cells would not be safe to be implanted into humans.

Martin, M., Muotri, A., Gage, F. & Varki, A. Nat Med. 2005 11, 1181:228-232